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THE CATALYTIC REDUCTION OF PARA DIMETHYLAMINOPHENOL

BY

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THESIS

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I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY Hermann Conrad Nies Heckel

ENTITLED The Catalytic Reduction of p-Dimethylaminophenol.

BE ACCEPTED AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE DEGREE OF Master of Science in Chemistry

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I wish to express my sincere thanks and appreciation to Professor Roger Adams for the suggestion of this problem and for the interest shown therein.

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I. INTRODUCTION

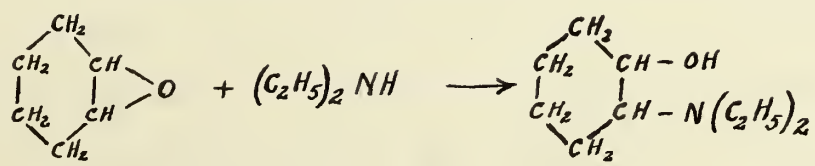
The object of this investigation was to develop a suitable method for the preparation of dialkylaminocyclohexanols.

The plan was to prepare these alcohols and then condense them with acid chlorides to give the esters of benzoic and p-aminobenzoic acids. These aminoalcohols, being aliphatic in nature, should produce esters which possess local anaesthetic properties, due to the similarity in structure with cocaine and novocaine.

It is hoped that within the next year the ortho, meta and para dimethylaminocyclohexanols as well as the diethyl derivatives will be prepared. This report, however, will deal only with a study of the preparation of p-dimethylaminocyclohexanol by the catalytic reduction of p-dimethylaminophenol. This aminoalcohol has not been prepared before, so that it is of interest to learn its physical constants.

II. HISTORICAL PART

To date, only one dialkylaminocyclohexanol has been prepared. L. Brunel (1) prepared o-diethylaminocyclohexanol by the action of diethylamine on the oxide of o-cyclohexanediol, the reaction proceeding as follows:



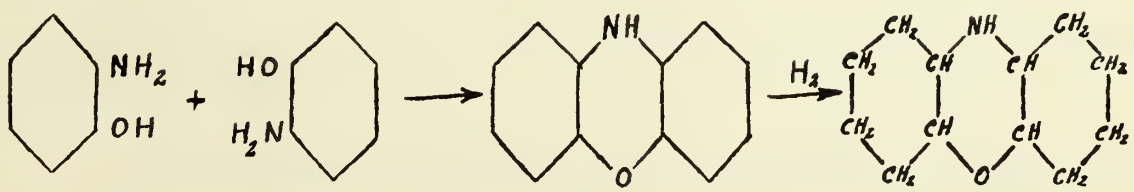
By similar reactions he also prepared o-aminocyclohexanol and o-ethylamino-cyclohexanol, using respectively, ammonia and ethylamine.

Osterberg and Kendall (2) also prepared o-diethylaminocyclohexanol. They, however, dehydrated cyclohexanol and obtained tetrahydrobenzene. To this they added hypochlorous acid giving o-chlorocyclohexanol, which was then condensed with diethylamine to give the desired compound.

In 1894 Noyes and Ballard (3) studied the action of nitrous acid on alkylamines. From 1.4 diaminocyclohexane they obtained p-aminocyclohexanol.

Skita and Rolfes (4), by means of colloidal platinum, reduced acetanilide, phenacetin and the acetotoluides to the corresponding acetylcyclohexylamines. Anisidine and phenetidine in the presence of hydrochloric acid gave both cyclohexylamine and dicyclohexylamine, the ethereal group being readily removed.

These authors also reduced the three aminophenols in the presence of acetic and hydrochloric acids. From the meta and para compounds they obtained both the mono- and dicyclohexylamines. With the ortho isomer, however, they also obtained dodekahydrophenoxazine, which probably results from the condensation of two molecules of o-aminophenol and the subsequent reduction of the condensation product.



These investigators did not attempt to stop at the aminoalcohol stage, but continued the reduction until the theoretical amount of hydrogen, necessary to carry the reduction to the cyclohexylamine stage, had been absorbed.

In a previous paper, Skita (5) observed that in reducing aniline by means of colloidal platinum in acetic acid solution, he could control to some extent the formation of the mono- and dicyclohexylamines, thru the addition of hydrochloric acid. The yield of monocyclohexylamine is thereby

increased.

As regards the hydrogenation of phenols by means of platinum to the cyclohexanol derivatives, not much work has been done. Vavon and Detrie (6) reduced phenol in glacial acetic acid solution using platinum black as the catalyst. They found that the reduction proceeded very readily. However, only a sixty-six percent yield of cyclohexanol was obtained, the remainder being further reduced to cyclohexane. These investigators further observed that the masking of the phenolic group, as for example, the formation of an ether, exerted a restraining influence upon the speed of the reduction. Experiments in this laboratory have shown that by means of platinum black, prepared by the fusion of chlorplatinic acid with sodium nitrate (15), phenol could be hydrogenated in alcoholic solution to give a theoretical yield of cyclohexanol, the hydrogen being absorbed very readily.

Further literature on the reduction of the benzene nucleus is very meager. In 1912 Willstatter and Hatt (7),using platinum black, reduced benzene, toluene and durol to the hexahydro derivatives. They also reduced phenol, obtaining results which are comparable to those of Vavon and Detrie, mentioned above. With aniline, Willstatter obtained a mixture of the mono- and dicyclohexylamines.

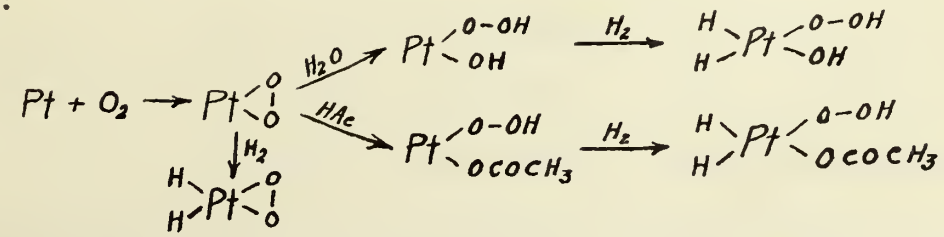
Skita and Meyer (8) reduced the benzene nucleus in benzene, toluene and benzoic acid thru the use of colloidal platinum. In reducing aromatic aldehydes, Skita and Brunner (9) observed that the reduction did not stop at the alcohol stage, but continued to the saturated hydrocarbon, the benzene nucleus being reduced as well as the alcohol group. Thus cinnamyl aldehyde gives both cyclohexylpropane and cyclohexylpropyl alcohol.

Willstatter and Jaquet (10) in 1918, published a paper concerning the hydrogenation of aromatic compounds by means of platinum containing oxygen.

They observed that in reducing phthalic and naphthalic anhydrides by the use of platinum black, the absorption of hydrogen stops after only a short time. The fact that the reduction begins at all seems to be due to the presence of oxygen in the fresh catalyst. Their experiments indicate that the two catalysts; namely, platinum containing oxygen and the same free from oxygen, are possessed of widely different characteristics. Thus, by the frequent loading of their catalyst with oxygen, they were able to hydrogenate phthalic anhydride, naphthalic anhydride and phthalimide with ease.

By completely exhausting the platinum of its oxygen, which these authors did by shaking the catalyst in an atmosphere of hydrogen for thirty hours, they were unable to reduce even such easily reduced compounds as the olefines. However, the need of oxygen in reductions seems to be dependent upon the ease of reduction of the substance in question. Thus, for the reduction of an olefine, the catalyst need not possess nearly so much oxygen as in the reduction of a benzene nucleus, due to the fact that the latter is so difficultly reduced. With such difficultly reduced substances, the oxygen content of the catalyst is very quickly depleted.

Willstatter in a very recent paper (11) explains catalytic reduction as due to the formation of a peroxide with the metal bivalent and then a combined hydride and peroxide with the metal quadrivalent, thereby effecting the transfer of the hydrogen. The following equations show the probable relations:



As the hydrogen is split off, some oxygen is also removed in the form of water, thus accounting for the well known fact that the catalyst slowly becomes in-

active. Shaking with air, however, will often revive its activity.

Skita (12) doubts the above mechanism due to the fact that in hydrogenating aromatic compounds by means of colloidal platinum, oxygen was found to be unnecessary. This investigator shook colloidal platinum in an atmosphere of hydrogen for thirty hours, as Willstatter had done with platinum black. Whereas Willstatter found his preparation was inactive, Skita observed that his would reduce phenol to cyclohexanol. Willstatter also observed that his active catalyst would set iodine free from iodides due to its oxidative properties. Skita, thereupon, added potassium iodide to a preparation of colloidal platinum, thus being assured of an oxygen free catalyst. At ordinary temperatures this catalyst proved inactive, but upon heating to 50-60° C. the reduction proceeded, but only one-eighth as fast as normally. These facts led Skita to believe the possibility of some other mechanism than the one mentioned above. He does not, however, claim to have proven that the above mechanism does not hold.

III. THEORETICAL PART

The only method which seemed at all promising for the preparation of this series of dialkylamino alcohols, especially as regards the preparation of the meta and para derivatives, was the catalytic reduction of the corresponding dialkylaminophenols thru the use of the platinum metals.

The only reported reduction of aminophenols led to the formation of mono- and dicyclohexylamine and in addition, in the case of the ortho isomer, dodekahydrophenoxazine. It was thus thought possible that the above reduction might be stopped at the alcohol stage after the theoretical absorption of hydrogen. Furthermore, since Skita observed that the addition of a small amount of hydrochloric acid hindered the splitting off of the amino residue,

and since the addition of the acid would make the base water soluble, it seemed advisable to work with the hydrochloride of the free base.

However, before the reduction of the hydrochloride was attempted, it seemed worth while to attempt the reduction of the free base. Thus, it was attempted to reduce p-dimethylaminophenol, both in aqueous suspension and in alcoholic solution. In the former case both colloidal platinum and platinum black were tried and in the latter case, platinum black alone was tried. In no instance, however, was the reduction successful.

As regards the reduction of the hydrochloride, it was found that the addition of the theoretical amount of hydrochloric acid to the free base was not effective, either with colloidal platinum, prepared by the method of Skita and Meyer (13) or with the black, prepared by the method of Feulgen (14) or by sodium nitrate fusion (15).

If, however, the free hydrochloride was first isolated by the precipitation of the base from dry ether by means of dry hydrochloric acid gas, the reduction did proceed, but only very slowly. With colloidal platinum the main product is dimethylaminocyclohexane, only a trace of p-dimethylaminocyclohexanol being obtained.

The next attempt was with platinum black prepared according to the method of Feulgen and it, too, proved a failure. In this case the reduction did not proceed at all. When platinum black, prepared by the sodium nitrate fusion method was used, the reduction was effected, but only very slowly. The platinum black at first seemed to form a colloidal suspension which was destroyed after the entrance of approximately one-half the theoretical amount of hydrogen. From this point on, no hydrogen was absorbed. The coagulation without doubt results from the cyclohexanol formed in the reduction. It was attempted to overcome this difficulty by using both 95 percent alcohol and 50 percent alcohol instead of water as the solvent. However, the attempts with

these two modifications proved no better than that in which water alone was used. The yield in all three cases was practically the same, consisting of approximately 20 percent p-dimethylaminocyclohexanol, 25 percent dimethylaminocyclohexane, and approximately 2 percent of cyclohexanol.

As stated above, the reduction proceeds very slowly. The probable cause for this is that p-dimethylaminophenol is very easily oxidized, its solution turning black even on standing in the air. The same applies to the hydrochloride. Since the aminophenol is so easily oxidized, the oxygen content of the platinum is very quickly depleted, thus causing the catalyst to lose its activity. This is substantiated to some extent by the fact that if fresh platinum black is added to a colorless solution of the hydrochloride in water, the latter being kept in an atmosphere of hydrogen, the solution will turn brown in the immediate vicinity of the catalyst. This indicates that an oxidation is taking place and seems to corroborate Willstatter's conclusions regarding the necessity of oxygen in active platinum. The platinum black in this case cannot be revivified by shaking with air as in the case of the reduction of many other organic compounds. The same explanation applies here; namely, the oxygen is taken from the platinum as fast as the latter absorbs it from the air. This seems to be substantiated by the fact that when the colorless solution and inactive catalyst are shaken with air the former quickly turns black.

That the amino group might exert a poisoning effect on the catalyst is very improbable, especially since in the above case it has been covered in the form of a hydrochloride. Certainly the phenolic group does not exert an undesirable effect, since phenol reduces with great ease.

The probable reason why the platinum black, prepared by sodium nitrate fusion, will effect the reduction, whereas that prepared by the method

of Feulgen will not, is because the former undoubtedly possesses much more oxygen. This explanation is supported by the fact that the former will reduce salicylaldehyde about twenty times as fast as the latter and will retain its activity much longer.

Since the alcohol group is reduced off to an extent of 50 percent, it seemed advisable to cover this group by some means, such that the free hydroxyl group could be easily regenerated. For this purpose the acetyl derivative of p-dimethylaminophenol was prepared. An attempt to reduce this substance in alcoholic solution, using the more active platinum black, prepared by sodium nitrate fusion, proved unsuccessful.

Thus, the only satisfactory method for reducing p-dimethylaminophenol seems to be the hydrogenation of the isolated hydrochloride in aqueous solution by means of platinum black prepared by the sodium nitrate fusion method. This study will be continued thru the coming year, and it is hoped that the method will be improved. This will probably be accomplished by the choice of a better solvent, since the latter seems to exert a strong influence upon the reduction.

IV. EXPERIMENTAL PART

A. Preparation of Catalysts

I. Colloidal Platinum

The colloidal platinum was prepared according to Skita and Meyer (13). One-half gram of gum arabic was dissolved in water by grinding in a mortar and adding from time to time a small amount of water. Then the desired amount of 10 percent chlorplatinic acid solution was added and the solution diluted to the desired volume. The resulting solution was inoculated by adding a small amount of colloidal platinum, prepared by reducing 0.5 to 1 cc.

of chlorplatinic acid in an alkaline solution with hydrazine hydrochloride or sulfate. This solution was shaken with hydrogen, whereupon the platinum was reduced, giving a colloidal solution. The substance to be reduced was then added.

II. Preparation of Platinum Black.

(a) Method of Feulgen (14)

Five grams of chlorplatinic acid was dissolved in 5 cc. of water, and to this was added 7 cc. of 40 percent formaldehyde solution. The latter was then cooled in an ice bath and a solution of 5 gr. of sodium hydroxide in 10 cc. of water was added drop by drop with vigorous stirring. Care should be exercised here as the reaction becomes vigorous and foams excessively upon too rapid an addition. The reaction mixture was allowed to stand for one-half hour at room temperature. The temperature was then raised to 55° C. and kept there for one-quarter hour, whereupon it was diluted with 250 cc. water. The mother liquor was decanted and more water added, the latter being acidified with acetic acid to prevent the formation of a colloidal suspension. The platinum black was finally filtered off and dried in vacuo over sulfuric acid.

(b) Sodium Nitrate Fusion Method (15)

Five grams of chlorplatinic acid was dissolved in 100-150 cc. of water and to this was added approximately 50 gr. of sodium nitrate. The solution was evaporated to dryness and then fused. It was kept at this temperature until the vigorous evolution of gas ceased. The melt was cooled and extracted with hot water. The platinum black was then filtered off, thoroughly washed and finally dried in vacuo over sulfuric acid. The final product is of a brown color and when shaken with hydrogen in an aqueous or alcoholic solution produces a colloidal suspension which will again coagulate upon shaking with air.

B. Preparation of p-Dimethylaminophenol and its Hydrochloride

To prepare the above the free base was first isolated from the oxalate salt which is obtained as a by-product in the manufacture of p-methylaminophenol, which is used as a developer.

To 182 gr. (0.5 mol.) of p-dimethylaminophenol oxalate was added enough water to make stirring easy. Forty gr. (1 mol.) of sodium hydroxide, dissolved in approximately 100 cc. of water, was added with vigorous stirring to prevent clumping. This mixture was extracted with benzene and then filtered. The benzene layer was separated and distilled in vacuo, the free base distilling over at 125° C. at about 7-8 mm. pressure. The distillate should be rapidly cooled as it oxidizes very readily upon exposure to air.

To prepare the hydrochloride the free base was dissolved in dry ether cooled in ice and dry hydrochloric acid gas passed in.At first the hydrochloride came down as a sticky mass which became crystalline as an excess of acid was passed in. The product was then filtered, washed with dry ether and finally dried in the air.

C. Preparation of Acetyl-p-dimethylaminophenol

The acetyl derivative of p-dimethylaminophenol was prepared by mixing together 30 gr. of the free base with 35 gr. of acetic anhydride and heating on the steam bath for one hour. The reaction mixture was then cooled and poured into a small amount of ice water. The product was filtered off, thoroughly washed with water and finally recrystallized from butyl alcohol, giving pretty pink crystals melting at 76° C.

D. Reduction Experiments

I. With p-Dimethylaminophenol

(a) Colloidal Platinum

To a preparation of colloidal platinum as described above and con-

taining 0.5 gr. platinum, 5 gr. of p-dimethylaminophenol was added and the volume of liquid increased to approximately 50 cc. Hydrogen was then passed in under a pressure of 30-35 lbs., but none was absorbed.

(b) Platinum black

To a suspension of 5 gr. of the free base in 50 cc. water was added 0.5 gr. platinum black, prepared by the sodium nitrate fusion method. The reaction mixture was then shaken for one hour with hydrogen under a pressure of 30-35 lbs. as above but no absorption took place. The same was repeated using 50 cc. of alcohol in place of the water, but with no better results.

Another series of experiments on the free base was tried. Here the theoretical amount of hydrochloric acid was added to take the base into solution. These attempts proved unsuccessful with colloidal platinum and the two platinum blacks.

The reduction of the acetyl derivative of p-dimethylaminophenol was attempted, using platinum black, prepared by the sodium nitrate fusion method and alcohol as the solvent. It likewise proved unsuccessful.

II. With p-Dimethylaminophenol Hydrochloride

(a) Colloidal Platinum

To a preparation of colloidal platinum, containing 0.5 gr. platinum, 12 gr. of free hydrochloride was added and the solution diluted to about 60 cc. This was then shaken with hydrogen under a pressure of 30-35 lbs. When approximately one-half the theoretical amount of hydrogen had been absorbed, the reaction stopped. The colloidal platinum was precipitated by acidifying strongly with hydrochloric acid and heating to boiling. The platinum was filtered off and the filtrate evaporated to 25-30 cc. in vacuo. Solid sodium hydroxide was then added to saturation and the basic layer extracted with ether or benzene. The extract was then distilled in vacuo, 5 gr. of dimethylamino-

cyclohexane, with a small amount of the desired alcohol, being obtained. The former distilled over at 52-54° C. at 17 mm. and the latter at 125° C.

(b) Platinum Black

To a solution of 12 gr. of the hydrochloride in 60 cc. of water was added 0.5 gr. of platinum black, prepared according to Feulgen. Hydrogen was then passed in under a pressure of 30-35 lbs., but no absorption took place.

The same was repeated, using 42 gr. of the hydrochloride in 120 cc. of water and 2 gr. of platinum black, prepared by the sodium nitrate fusion method. The reduction proceeded, but only very slowly. As with colloidal platinum, the absorption stopped in midreaction. To attain this stage required from 10 - 14 hrs. At this point the platinum black, which at first assumed a colloidal state, flocked out. Upon working up the reaction mixture as before 11 gr. of dimethylaminocyclohexane, 3 gr. of cyclohexanol and 8 gr. of p-dimethylaminocyclohexanol were obtained. The cyclohexanol steam distilled over upon evaporating the solution in vacuo. The p-dimethylaminocyclohexanol distilled over at 99.5 - 100° at 7 mm. pressure.

Similar runs were made using 95 percent and 50 percent alcohol as the solvents. The results were practically the same as those obtained above.

E. Description of Products

I. Dimethylaminocyclohexane

This compound has already been prepared but its physical constants do not agree closely with those reported in the literature. Therefore, it seemed of value to determine the following constants:

(1) Boiling Point ..... 160° C.

(2) Specific Gravity ..... 0.847 $\frac{25^\circ}{25^\circ}$

(3) Index of Refraction ($N_D^{24^\circ}$) 1.4528

The hydrochloride upon recrystallization from butyl alcohol melted at 238° C.

Analysis: Subs. 0.3093 gr., 17.00 cc. 0.1096N $AgNO_3$

Calc. for $C_8H_{17}N.HCl$: Cl, 21.69%, Found: 21.36%

Subs. 0.4793 gr., 43.71 cc. 0.0843N acid,

Calc. for $C_8H_{17}N$: N, 11.02%, Found: 10.76%

II. p-Dimethylaminocyclohexanol

As stated above, this substance has never been prepared before. It is a colorless and very viscous liquid possessing the following physical constants:

(1) Boiling Point ..... 228° C.

(2) Specific Gravity ..... 0.983 $\frac{25°}{25°}$

(3) Index of Refraction ($N_D^{24°}$) 1.4859

The hydrochloride is very hygroscopic. Indeed, it absorbs moisture from the atmosphere so fast that it is impossible to get the substance into a melting point tube. After careful drying in a vacuum oven at 100° C. it was analyzed. Analysis:

Subs. 0.2844 gr., 14.53 cc. 0.1096 N $AgNO_3$

0.4702 gr., 34.3 cc. N_2 (32° C., 739.4 mm.)

Calc. for $C_8H_{17}ON.HCl$: Cl, 19.85%; N, 7.80%,

Found: Cl, 19.76%; N, 7.72%

V. SUMMARY

The reduction of the hydrochloride of p-dimethylaminophenol was effected catalytically by means of platinum black, prepared by the fusion of chlorplatinic acid with sodium nitrate.

The products of the above reduction in aqueous solution, consisted of approximately equal amounts of p-dimethylaminocyclohexanol and dimethylaminocyclohexane.

The observations led to the conclusion that the slowness with which the reduction proceeds was due to the fact that the oxygen content of the platinum was very quickly and seriously depleted by the easily oxidizable p-dimethylaminophenol hydrochloride.

p-Dimethylaminocyclohexanol, which has not been previously described, was obtained as a colorless, viscous liquid and its physical constants were determined.

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